BIOLOGICAL EFFECTS OF PROTONS AND NEUTRONS IN LARGE ANIMALS*

S. Tom Taketa

Environmental Biology Division
National Aeronautics and Space Administration
Ames Research Center, Moffett Field, California

ABSTRACT

This report is concerned primarily with the biological effects of protons in large animals. Pertinent neutron data are also discussed. A review of the literature reveals only a limited number of large animal proton studies. This is not surprising because of the difficulties involved in exposing large animals to whole body proton irradiation in ground-based facilities.

Studies were undertaken, in collaboration with Drs. Tobias and Sondhaus of the University of California, Berkeley, to determine biological effects of high energy protons compared to Co-60 gamma-rays in whole body irradiated monkeys. The 730 MeV protons of the Berkeley 184-inch cyclotron were degraded to the desired 200 MeV energy level by multiple Coulomb scattering. In addition to causing angular divergence of the emergent beam which provided the desired effective exposure field for whole body irradiation of large animals, the use of scatters allowed us to study the combined effects of the attenuated primary proton flux and the induced secondary radiations,

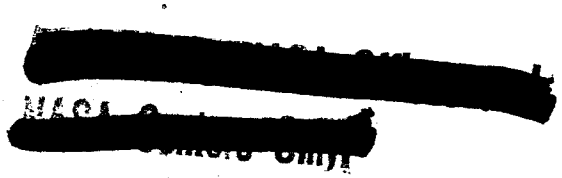
*Presented by invitation at the Second Symposium on Protection Against Radiations in Space, Gatlinburg, Tennessee, October 1964.

[redacted]

hence simulating a more realistic situation which an occupant of a spacecraft may encounter. The exposure set-up employed was unique in that it provided omnidirectional exposure. This was accomplished by rotating the animal, strapped in a styrofoam holder, simultaneously around its longitudinal and vertical axes. Proton exposures ranged from 200 to 950 rads midpoint air dose; gamma exposures, 195 to 1065 rads. Dose rate for protons, 7 meters from the beam port, was about 20 rads per minute. A comparable dose rate for gamma rays was obtained at midpoint to source distance of 114 cm. Depth-dose profiles were determined in a frozen monkey, using LiF dosimeters.

The results of depth-dose measurements showed (1) a dose fall-off at midpoint in gamma exposures, but a dose build-up in proton exposures; (2) tissue doses at various loci varied, with respect to the midpoint dose, from 96 to 114 percent and 71 to 104 percent in gamma and proton exposures, respectively; and (3) the midpoint tissue dose (MTD) was 60 to 70 percent of midpoint air dose (MAD) in gamma exposures, and about 120 to 130 percent in proton exposures, indicating that for a given MAD, the MTD for protons was about twice that for gamma rays.

The relative biological effectiveness (RBE) of protons was compared with gamma rays for lethality and white blood cell (WBC) depression. The RBE's were based on both MAD and MTD data for comparison with values in the literature, and to point out the discrepancies that could arise when data based on exposure (air) dose instead of tissue dose are used. It is suggested that a more



accurate comparison, for the biological endpoints considered, might be based on average body dose (ABD). The minimal lethal doses for gamma- and proton-irradiated animals, based on MAD, MTD, and ABD were 485 and 500 rads, 325 and 650 rads, and 340 and 565 rads, respectively, giving RBE's of 1, 0.5, and 0.6, respectively. The MAD's, MTD's, and ABD's to cause 80 percent WBC depression in gamma- and proton-irradiated animals were 290 and 200 rads, 190 and 250 rads, and 210 and 235 rads, respectively, for RBE's of 1.4, 0.7, and 0.9, respectively. The survival times of the decedents were essentially similar for the two types of radiation and ranged predominantly from the 10th to the 20th post-exposure days, which suggests prominence of the hematological syndrome.

The dose-response patterns of peripheral white blood cell (WBC) counts in animals given exposures of 500 rads and below were of interest. It was observed (1) that the rate of depression appeared to be slower in proton animals even though the maximum level of depression was greater than in gamma animals; (2) the rate of recovery was fastest in both proton and gamma animals given the highest dose, and slowest in those given the lowest dose; and (3) that a more permanent depression, maintained at about 50 to 75 percent of pre-exposure values occurred from about the 50th to 60th post-exposure days in proton animals.

It is concluded on the basis of existing MTD data (1) that for hematological effects, the effectiveness of high energy protons in large animals may be somewhat less than that of gamma rays, X-rays,

or fast neutrons, and (2) that appropriate experimental data are lacking to even consider a maximum permissible emergency exposure for space explorers. The need to determine the effectiveness of protons, alpha particles, and other radiations prevalent in space on large animals, and to study combined stress effects, using sublethal doses, for establishing reasonably realistic exposure tolerance limits, is discussed.

BIOLOGICAL EFFECTS OF PROTONS AND NEUTRONS IN LARGE ANIMALS

S. Tom Taketa

Environmental Biology Division
National Aeronautics and Space Administration
Ames Research Center, Moffett Field, California

INTRODUCTION

The hazard of radiation in space is of sufficient magnitude to require protective measures in manned spacecraft (Foelsche, 1963; McDonald, 1963; Freier and Webber, 1963). The contributions of physicists, engineers, and life scientists are all essential in resolving this requirement. It is not an easy task because numerous uncertainties still persist, relating not only to environmental data and techniques for shielding calculations, but also to a permissible emergency exposure for man in space. The lack of pertinent experimental data precludes establishment of such a permissible dose level at present.

The biological effectiveness of protons - potentially the greatest radiation hazard known to exist in space - in man is unknown. It is unlikely that man himself will be purposely exposed

---

Abbreviations used in this report:
gamma animal = gamma-irradiated animal; proton animal = proton-irradiated animal; ABD = average body dose; MAD = midpoint air dose; MTD = midpoint tissue dose; RBE = relative biological effectiveness; WBC = white blood cells.

to protons for assessment of their injurious effects. Consequently, the information must be derived from animal experimentation. Although extrapolation of animal data to man obviously has its limitations, past experience with other types of radiation has shown that valuable and useful information can be obtained from such animal studies (Bond, 1960).

This report is concerned primarily with the biological effects of protons in large animals. Pertinent neutron data will also be included. A review of the literature shows only a limited number of large animal proton studies. This is not too surprising because of the difficulties involved in exposing large animals to whole body proton irradiation in ground-based facilities. Relevant experimental proton data were presented at the Symposium on the Biological Effects of Neutron and Proton Irradiations (Komarov, 1964; IAEA, 1964a, 1964b).

The results presented in this report are from the collaborative studies currently under way between NASA, Ames Research Center, and Lawrence Radiation Laboratory, University of California, Berkeley, to determine the biologic effectiveness of protons compared to other types of radiation in rhesus monkeys. They indicate that under our experimental conditions 200 MeV protons are less effective than 1.2 MeV Co-60 gamma rays in causing lethality or white blood cell depression in whole body irradiated monkeys.

METHODS AND MATERIALS

Animals.- Young adult male monkeys (M. mulatta) commercially imported from India and weighing about 4 to 6 kg at exposure time were used. The animals, which were quarantined for at least two months after arrival, underwent the usual routine treatment preparatory to their use (Gisler, 1960). Blood for routine hematological studies (and occasional bacteriological cultures) was taken from the femoral veins. For pre-exposure hematological control values, blood samples were taken from each animal three to four times over a period of one month prior to irradiation. The frequency after irradiation was once every three to four days during the first post-exposure month and once every week or two thereafter. For exposure, the animals were sedated with thiamylal sodium, a short acting anesthetic, strapped in a styrofoam animal holder, and placed on a rotator which turned the animal simultaneously around its longitudinal and vertical axes to provide an omnidirectional whole body exposure (see Sondhaus, 1962, 1964a). The rates of rotation were 8 and 0.35 rpm, respectively. The animals were conscious throughout the exposure period which lasted about 10 to 60 minutes, depending upon the exposure dose. Nonirradiated control animals were treated similarly.

Exposure set-up and dosimetry.- For proton exposure, the 730 MeV protons of the Berkeley 184-inch cyclotron were degraded to the desired 200 MeV energy level by multiple Coulomb scattering

which was accomplished by placing 42 inches of graphite between the path of the primary 730 MeV beam and the animal. This caused angular divergence of the emergent beam and provided the desired effective exposure field for whole body irradiation of monkeys. Dosimetric measurements indicated that the exposure dose at the perimeter of the effective 60 cm field at 7 meters from the beam port was about 70 percent of that at the center. Dose rate at the center was about 20 rads per minute. Figure 1 shows an animal positioned for exposure to protons. The Co-60 radiation source at Berkeley was used for gamma exposure. A dose rate comparable to that of protons was obtained at a distance of 114 cm.

A reasonably flat, similar depth-dose profile for proton and gamma exposures was achieved by positioning the rotator in such a manner that the rate of vertical (sinusoidal) rotation (see Fig. 17, Sondhaus, 1962) was minimal when the animal's longitudinal axis was parallel to the beam for exposure to protons, and perpendicular, for exposure to gamma rays.

Surface doses were determined for each irradiated animal with dosimeters (polyethylene capsules filled with lithium fluoride) placed on the head, abdomen, arm and leg. Depth-dose measurements were made in a frozen monkey cadaver in which dosimeters were placed on the surface and at varying depths at several loci. The exposure geometry of the cadaver was identical to that of live animals, except perhaps for head movements of the latter. LiF dosimeters were used because of their convenience and reliability (Cameron, 1964; McCall, 1963; Tochilin, 1963).

RESULTS

Dosimetry.- The results of the depth-dose measurements are summarized in Figure 2a, in which the data are presented as percent of midpoint tissue dose. The numerator at each point is the dose for gamma animals, the denominator, for proton animals. The doses listed outside the animal are surface doses; those presented inside the animal immediately adjacent to the surface are doses at 1 to 2 cm depth; and those given in the center of the animal and in the limbs are midaxial doses. The midpoint dose is lower than in the extremities, including the head, in gamma animals indicating a depth-dose fall off; whereas, the midpoint dose is higher than in the extremities in the proton animals indicating a dose build-up. The depth-dose profile shows that the tissue doses throughout the animal with respect to the midpoint dose varied from 96 to 114 percent in gamma animals, and from 71 to 104 percent in proton animals.

The midaxial dose profile is shown in Figure 2b. The midaxial trunk dose distribution was fairly uniform (or flat) for both gamma and proton animals. However, the doses in the head and in the lower hindlegs were about 10 percent higher than at the midpoint in gamma animals, and about 20 percent lower in proton animals.

The cross-sectional depth-dose profile at the midpoint level is illustrated in Figure 2c. It is evident that the MTD was about 8 percent lower than the dose at the surface in gamma animals, and about 3 to 6 percent higher in proton animals.

A comparison of MAD with MTD reveals that the latter is about 60 to 70 percent of the former in gamma animals, and about 120 to 130 percent in the case of proton animals. This means that for a given MAD, the MTD for protons is about twice that for gamma rays.

Mortality and survival time.- Table 1 summarizes the mortality and survival time data. When based on MAD, the minimal lethal doses for gamma and proton animals were essentially similar - 485 and 500 rads, respectively - giving a RBE of about 1. However, when based on MTD, the respective minimal lethal doses were 325 and 650 rads for a RBE of 0.5. The survival times of decedents were similar for the two types of radiation and ranged predominantly from the 10th to the 20th post-exposure days, which suggests prominence of the hematological syndrome (Allen, 1959; Cronkite, 1956).

White blood cell response.- Changes in peripheral white blood cell count, a fairly reliable and sensitive index of hematopoietic tissue injury in whole body irradiated animals, were used to assess the effectiveness of protons compared to gamma rays. Figure 3 shows a radiation dose-WBC response pattern in our proton monkeys. Figures 4a, 4b, and 4c compare the WBC patterns in proton and gamma animals given 200, 350, and 500 rads air dose, respectively. Each line represents a single animal. As expected, the destructive phase was dose dependent in both gamma- and proton-irradiated animals. Although the rate of WBC depression was faster in gamma- than in proton-irradiated animals at all three dose levels, the

magnitude of the depression was greater in the proton animals (see Figs. 4a, 4b, 4c). WBC recovery in proton survivors was fastest in animals given the highest dose of radiation and slowest in those given the lowest dose (Fig. 3). This was unexpected, since in general the rate of recovery is indirectly related to the magnitude of injury, which in turn is directly related to dose (Cronkite, 1955; Smith, 1963). This unexpected response was also seen in our gamma animals. A second, more permanent WBC depression to about 50 to 75 percent of pre-exposure values occurred from about the 50th to the 60th post-exposure days in proton animals. This depression was not readily apparent in the gamma animals.

The relationship between radiation dose and magnitude of maximum WBC depression was determined for gamma and proton animals. The data are tabulated in Table 2 and the mean values are graphically presented as logarithmic probability plots in Figures 5a and 5b. The maximum WBC depression for each animal was obtained by averaging several observations during the critical period, ranging from about the 6th to the 15th post-exposure days. The values given in the INCIDENCE column of Table 2 are the average depressions so obtained; each value represents the depression for a single animal. The values given in the MEAN column are the averages of the values given in the INCIDENCE column. It is obvious that when based on exposure dose (MAD), protons were more effective in causing WBC depression than gamma rays. However, when based on tissue dose (MTD), gamma rays were more potent than protons. For example, an exposure

dose of 290 rads gamma rays compared to 200 rads proton was required to cause an 80 percent depression in WBC (see Fig. 5a), giving a RBE of about 1.4. The respective tissue doses (MTD) were 190 and 250 rads (see Fig. 5b), for a RBE of about 0.7.

Effectiveness of protons and neutrons in large animals.- Table 3 summarizes some of the pertinent proton and neutron studies in large animals. The three biological endpoints considered here have one thing in common - involvement of hematopoietic tissues. Hence, the RBE's apply primarily to hematologic effects of ionizing radiation. The effectiveness of fission neutrons, simulated fission neutrons and protons have been compared with X-rays or gamma rays in dogs, monkeys, and in one case, goats. Acute, single exposure doses were used in all studies except by Baum (1961), who compared the effect of four fractionated doses (150 rads per exposure, spaced 3 months apart) of simulated fission neutrons and gamma rays on erythropoietic recovery, as measured by Fe-59 uptake.

The studies of Alpen (1960), Baum (1961), Bond (1956), and Grigor'ev (1964) were similar in that they compared the effects of fast neutrons or protons with X-rays in dogs. The first three investigators reported RBE's of about 1 for neutrons, based on MTD data; the fourth, a RBE of 1 for protons. However, it was not clear whether the latter was based on air or tissue dose.

The studies of Pickering (1963), Zellmer (1962), and Taketa (this study) were comparable to the extent that they compared the effects of fast neutrons or protons with gamma rays in rhesus

monkeys. Although it was not clear whether the first two based their RBE's on MAD or MTD data, it is known that they used the same basis, whichever it was. Their RBE values of 1.3 and 1.6 for neutrons and protons, respectively, suggest that protons may be as effective as neutrons. Taketa's RBE's of 1 and 1.4 for data based on MAD are not too different from those of Pickering (1963) and Zellmer (1962). However, Taketa's RBE's of 0.5 and 0.7, based on MTD, are lower by a factor of 2 to 3.

A comparison of the RBE values in Table 3 based on MTD data (Alpen, 1960; Baum, 1961; Bond, 1956; and Taketa, this study) indicates that high energy protons are less effective than gamma rays, X-rays, or fast neutrons for hematologic effects. The magnitude of the differences between protons and X-rays and neutrons is actually greater than is apparent here, when we consider that X-rays with which neutrons were compared are more effective than the proton-compared gamma rays (see Bond, 1957b).

DISCUSSION

The action of high energy protons, as was used in this study, differs from commonly used lower energy gamma- and X-rays in that they induce dose build-up during passage through matter including tissue. This phenomenon, which was apparent in depth-dose measurements made in the present study, is particularly evident in large animals, since the dose build-up is related to the distance in tissue traversed by the primary protons. This increase in tissue

dose is independent of the Bragg peak effect of the incident protons and is undoubtedly due to the production of secondary protons (elastic, cascade, and evaporation protons; Wallace, 1964) and smaller numbers of other particles including electrons, mesons, recoil nuclei, and neutrons.

The importance of depth-dose measurements, particularly in large animals, cannot be overemphasized (Bond, 1957a, 1957b; Moskalev, 1964). This is especially true when the degree of discrepancy between air and tissue dose differs greatly for the radiations being considered. For example, in the present study the MTD was 60 to 70 percent of MAD for gamma rays, and 120 to 130 percent for protons. Hence, for a given air dose (MAD), the tissue dose (MTD) in a proton animal was about twice that in a gamma animal. This difference was apparent in the RBE values for lethality and WBC depression, which differed by a factor of 2 when based on MAD (1 and 1.4) compared to MTD (0.5 and 0.7).

The discrepancy of 30 to 40 percent between MAD and MTD in our gamma animals is considerably larger than values reported by others. For instance, Baum (1961) found midline tissue dose to be 17 percent lower than midline air dose in bilaterally irradiated dogs. Bond and Robertson (1957b) concluded that tissue dose is approximately equal to air dose in medium-sized species such as rabbit and monkey, given either bilateral exposure or lateral exposure with rotation along the long axis. The difference in ratio of air dose to tissue dose reported here compared to others could be explained, at least in part, on differences in exposure geometry, which is

considered to influence greatly the relationship between air and tissue dose (Bond, 1957a, 1957b). It will be recalled that our exposure set-up was unique in that the animal was rotated simultaneously around its longitudinal and vertical axes for omnidirectional exposure.

Although we based our RBE values on both MAD and MTD data for a comparison with the values in the literature, and to point out the discrepancies that could arise when data based on air dose instead of tissue dose are used, a more meaningful comparison might have been based on average body dose (ABD). The reason for this is that tissue dose at midpoint was essentially the lowest for gamma rays and highest for protons. Hence, RBE's based on MTD data were actually comparisons of extreme dose values, which were not necessarily representative of doses delivered to hematopoietic tissue - the tissue of interest in this study. Since hematopoietic tissue is found at various depths and loci, it seems that ABD may be a more realistic basis for RBE determination than MTD.

In order to compare the RBE's based on MTD data with those based on ABD, the ABD's for tissue doses listed in Figure 2 were calculated. It was found that for gamma exposures ABD was about 5 percent higher than MTD, and for protons, about 13 percent lower. The minimal lethal ABD's for gamma and proton animals were 340 and 565 rads, respectively, for a RBE of 0.6 (compared to 0.5 based on MTD data). The ABD's required to cause 80 percent WBC depression in gamma and proton animals were 210 and 235 rads, respectively, for a RBE of about 0.9 (compared to 0.7 based on MTD data).

It is of interest that the RBE values of 0.5 to 0.6 for lethality and 0.7 to 0.9 for WBC depression found in this study were not too different from those given by Stapleton (1964) for protons ranging in energy from a few MeV to 730 MeV on simple cellular systems, when the lower effectiveness of gamma rays to X-rays is taken into account.

Three observations involving WBC responses in proton and gamma animals are worthy of comment. The first concerns the observation that the rate of depression appeared to be slower in proton animals even though the maximum level of depression was greater than in gamma animals (see Figs. 4a, 4b, 4c). The latter response is apparently due to the higher tissue dose in proton than in gamma animals; however, this does not explain the slower rate of depression. The second concerns the observation that the rate of recovery was fastest in animals given the highest dose, and slowest in animals given the lowest dose (Fig. 3). This phenomenon was also observed in gamma animals. The reason for this unexpected response is not known. Since it is apparently related to greater injury, it may involve infection, but not necessarily bacteremia. The third concerns the observation of a second, more permanent depression, maintained at about 50 to 75 percent of pre-exposure values, from about the 50th to 60th post-exposure day especially in proton animals. The significance of this low WBC level is not known. Studies are in progress to determine the response of these animals to induced infection.

The data considered so far have been concerned with the effectiveness of highly energetic protons on hematological tissue in large animals. Now, let us consider other biological effects of protons in large animals. Investigators at the USAF School of Aerospace Medicine, Brooks AFB, Texas, have undertaken studies to determine the biologic effects of monoenergetic protons ranging in energy from 14 MeV to 730 MeV in monkeys. In addition to the data presented in Table 3, Pickering (1963) and Zellmer (1961) reported RBE values of 1 for iridocyclitis and erythema, and 2 for epitation and desquamation in focal eye-irradiated monkeys exposed to 14, 39, 185, and 730 MeV protons (compared to Co-60 gamma rays). Rexford-Welch (1964) reported that in similarly irradiated animals, 730 MeV protons induced cataracts in 12 to 18 months at doses as low as 750 rads, whereas lower energy protons (14, 40, and 187 MeV) were ineffective even at doses as high as 2000 rads. This observation of cataractogenesis in high energy but not in low energy protons is of interest, since, for fast neutrons, damage to the lens is generally considered to be less pronounced with increasing energies (Lushbaugh, 1957). Rexford-Welch also reported that death in the 187 MeV proton animals occurred in 100 to 200 days after exhibiting central nervous system (CNS) symptoms. Lindsay (personal communication) found that 6000 rads of 40 MeV protons to the whole body (given in two parts - upper and lower halves) caused convulsive seizures and death in about 48 hours following exposure, suggesting a CNS radiation effect. Admittedly the

doses to produce the CNS effects were high, but the results are interesting and significant. Pickering (1963) had expressed concern of possible latent or long-term effects based on his observation of a gradual onset of lethargy, anorexia, and ataxia exhibited among survivors of whole body proton-irradiated animals at 2-1/2 to 5-1/2 months post-irradiation. We have not observed these effects so far in any of our 5 to 6 month irradiated survivors.

A limited number of Russian reports involving large animal proton exposures have appeared. In addition to the data presented in Table 3, Grigor'ev (1964) claimed that hemorrhage appeared earlier and was severer in proton- compared to x-irradiated dogs. We have not observed any striking difference between proton- and gamma-irradiated monkeys at necropsy. A large animal (dog) exposure facility has been described by Afanas'yev (1964), and the literature on the biological effects of neutrons and protons has been reviewed by Moskalev (1964).

The existing MTD data suggest that, in general, the effectiveness of high energy protons in large animals may be less than that of gamma rays, X-rays, or fast neutrons. Whether this also applies to man is not known, since species differences are known to exist (Bond, 1957b; Cronkite, 1956; Leong, 1963; Patt, 1963). Protons, like neutrons, have a preferential intestinal effect in whole body irradiated mice (Ashikawa, 1964; Sondhaus, 1964b). It is clearly evident that additional data in several mammalian species are needed before extrapolation to man can even be considered.

Before proceeding with a discussion as to the types of studies that are needed, let us first consider the criterion on which maximum permissible emergency exposure for man in space is to be based. It seems logical, as suggested by Schaefer (1961) and expanded by Grahn (1964), that exposure should be kept below the level of acute injury and incapacitation effects which would impair performance. The criterion is then, performance. The question remains, "What level of performance?" This is important, since success of a space mission may depend to a large extent upon the level of performance required of an astronaut. An example of the types of questions that should be considered is, "Would nausea impair the level of performance sufficiently to jeopardize the mission?"

Studies should be oriented to determine the exposure tolerance limits for performance capabilities required. It means studying sublethal as well as protracted dose effects, using both uniform and nonuniform (solar flare-type) depth-dose profiles. Biologic effects peculiar to ionizing radiations prevalent in space, particularly protons and alpha particles, should be determined and studied in detail to assess their significance. Examples of such effects observed in the present study have already been discussed; they involved apparent differences in the rates of WBC depression and recovery in proton compared to gamma animals. A realistic approach is to study in ground-based facilities not only the effects of radiation, but also the combined effects of radiation and other stresses associated with space travel. (The influence of

weightlessness as a variable would require studies in space.) Many of the nonradiation effects can be determined in man himself. However, chronic, long term studies, and especially those involving ionizing radiation require animal experimentation. Valuable data on radiation effects in man can be extracted from clinical radiation exposures (see Bond, 1960; Cronkite, 1960). However, pertinency of the data so obtained will depend upon the performance required.

ACKNOWLEDGMENT

The author gratefully acknowledges the interest and support shown by Cornelius A. Tobias of the Lawrence Radiation Laboratory, the valuable advice and assistance given by Eugene Tochilin and Catherine L. Wingate of the United States Naval Radiological Defense Laboratory on LiF dosimetry, and the active participation of Charles A. Sondhaus (LRL), Bruce L. Castle and Wayne H. Howard in the experimental study described herein.

This study was supported by the National Aeronautics and Space Administration, partly through the Atomic Energy Commission and Lawrence Radiation Laboratory.

REFERENCES

Afanas'yev, V. P., I. B. Keirim-Markus, S. S. Kuznetsova, E. G. Litvinova, I. K. Sokolova, and L. Ye. Stukina (1964), The Generation and Investigation of Field Doses for Irradiation of Experimental Animals with High-Energy Protons, (in Russian) (see Reference IAEA, 1964a, pp. 71-90). (English translation: FTD-TT-63-1048; Foreign Tech. Div., AF Systems Command, Wright-Patterson AFB, Ohio, March 2, 1964.)

Allen, R. G., Jr., F. A. Brown, L. C. Logie, D. R. Rovner, S. G. Wilson, Jr., and R. W. Zellmer (1959), Acute Effects of Gamma Radiation in Primates, Sch. of Avia. Med., USAF, Randolph AFB, Texas, AFPS SA Apr. 60, 200 (59-41), pp. 1-23.

Alpen, E. L., O. S. Shill, and E. Tochilin (1960), The Effects of Total Body Irradiation of Dogs with Simulated Fission Neutrons, Rad. Res., 12:237-250.

Ashikawa, J. K., C. A. Sondhaus, C. A. Tobias, A. G. Greenfield, and V. Paschkes (1964), Difference in Injury Mode, Dose-Rate Dependence and RBE of 730-MeV Protons, 100-kVp X-Rays, and 250-kVp X-Rays, (see Reference IAEA, 1964a, pp. 249 - 260).

Batchelor, A. L., and P. W. Edmondson (1964), Fast-Neutron Irradiation of Large Animals, (see Reference IAEA, 1964b, pp. 3-13).

Baum, S. J., A. K. Davis, and E. L. Alpen (1961), Effect of Repeated Roentgen or Neutron Irradiation on the Hematopoietic System, Rad. Res., 15:97-108.

Bond, V. P., R. E. Carter, J. S. Robertson, P. H. Seymour, and H. H. Hechter (1956), The Effects of Total-Body Fast Neutron Irradiation in Dogs, Rad. Res., 4:139-153.

Bond, V. P., E. P. Cronkite, C. A. Sondhaus, G. Imirie, J. S. Robertson, and D. C. Borg (1957a), The Influence of Exposure Geometry on the Pattern of Radiation Dose Delivered to Large Animal Phantoms, Rad. Res., 6:554-572.

Bond, V. P., and J. S. Robertson (1957b), Vertebrate Radiobiology (Lethal Actions and Associated Effects), Ann. Rev. of Nucl. Sci., 7:135-162.

Bond, V. P., T. M. Fliedner, and E. P. Cronkite (1960), Evaluation and Management of the Heavily Irradiated Individual, J. of Nucl. Med., 1:221-238.

Cameron, J. R., D. Zimmerman, G. Kenney, R. Buch, R. Bland, and R. Grant (1964), Thermoluminescent Radiation Dosimetry Utilizing LiF, Health Physics, 10:25-29.

Cronkite, E. P., and G. Brecher (1955), The Protective Effect of Granulycytes in Radiation Injury, Ann. N.Y. Acad. Sci., 59:815-833.

Cronkite, E. P., and V. P. Bond (1956), Effects of Radiations on Mammals, Ann. Rev. Physiol., 18:483-526.

Cronkite, E. P., and V. P. Bond (1960), Radiation Injury of Man. Its Biological, Chemical and Pathological Basis, C. C. Thomas Co., Springfield, Ill.

Foelsche, T. (1963), Estimates of Radiation Doses in Space on the Basis of Current Data, 3rd Internat. Space Sci. Symp., Life Sciences and Space Research, Washington, D. C., April 30-May 9, 1962, North-Holland Publ. Co., Amsterdam, pp. 48-94.

Freier, P., and W. R. Webber (1963), Radiation Hazard in Space from Solar Particles, Sci., 142:1587-1592.

Gisler, D. B., R. E. Benson, and R. J. Young (1960), Colony Husbandry of Research Monkey, Ann. N.Y. Acad. Sci., 85:758-768.

Grahn, D. (1964), Methods in the Evaluation of Radiation Hazards in Manned Space Flight, this Symposium.

Grigor'ev, G., N. G. Darenskaya, M. P. Domshlak, A. V. Lebedinskii, G. Nefedov, and N. I. Ryzhov (1964), Characteristics of the Biological Action and Relative Biological Effectiveness of High-Energy Protons, (in Russian) (see Reference IAEA, 1964a, pp. 223-230), English translation: AEC-Tr-6444, 1964.

IAEA (1964a), Proc. Symp. Biological Effects of Neutron and Proton Irradiations, Oct. 7-11, 1963, Upton, N.Y., vol. I, pp. 433 (March), Internat. Atomic Energy Agency, Vienna.

IAEA (1964b), Proc. Symp. Biological Effects of Neutron and Proton Irradiations, Oct. 7-11, 1963, Upton, N.Y., vol. II, p. 446 (May), Internat. Atomic Energy Agency, Vienna.

Komarov, E. (1964), Biological Effects of Neutron Irradiations, Report on Internat. Symp. Brookhaven National Laboratory, Oct. 7-11, 1963, Atomic Energy Review, 2:65-78.

Leong, G. F., W. G. Wisecup, and J. W. Grisham (1963), Effects of Divided Doses of X-Ray on Mortality and Hematology of Small and Large Domestic Animals, USNRDL-TR-606, (Jan.), p. 22.

Lushbaugh, C. C. (1957), Vertebrate Radiobiology (The Pathology of Radiation Exposure), Ann. Rev. Nucl. Sci., 7:163-184.

McCall, R. C., L. E. Babcock, and R. C. Fix (1963), LiF Thermo-luminescent Dosimeter System for Radiation Research, Rad. Res., 19:200.

McDonald, F. B. (1963), Solar Proton Manual, NASA TR R-169, p. 117.

Moskalev, I. (1964), Some Results of the Study of the Biological Effect of Neutrons and Protons, (in Russian) (see Reference IAEA, 1964a, pp. 181-193). (English translation: FTD-TT-63-1046, Foreign Tech. Div., AF Systems Command, Wright-Patterson AFB, Ohio, April 27, 1964).

Patt, H. M., and M. A. Maloney (1963), A Comparison of Radiation-Induced Granulocytopenia in Several Mammalian Species, Rad. Res., 18:231-235.

Pickering, J. E. (1963), Biological Effects of Whole Body Proton Irradiation, Aerospace Med., 34:942-943.

Rexford-Welch, S. C. (1964), Clinical Effects Consequent on the Exposure of Mammalian Ocular Tissues to High-Energy Protons (see Reference IAEA, 1964a, pp. 287-295).

Schaefer, H. J. (1961), Radiation Tolerance Criteria in Space Operations, U.S. Naval Sch. of Avia. Med., U.S. Naval Avia. Med. Ctr., Pensacola, Florida, Rep. No. 20, Sept. 1, 1961.

Smith, W. W., I. M. Alderman, C. A. Schneider, and J. Cornfield (1963), Radiation Dose-Response Characteristics of Leucocyte Recovery in the Mouse, Proc. Soc. Exp. Biol. Med., 113:1016-1018.

Sondhaus, C. A. (1962), Biological Effects of High-Energy Protons, Proc. Symp. Protection Against Radiation Hazards in Space, Nov. 5-7, Gatlinburg, Tenn., TID-7652, Book 1, pp. 309-342.

Sondhaus, C. A., R. W. Wallace, J. T. Lyman, K. W. Kase, and P. G. Steward (1964a), Physical Parameters in Exposure of Large Animals to High-Energy Protons (see Reference IAEA, 1964a, pp. 231-247).

Sondhaus, C. A. (1964b), Effects of High-Energy Protons and Alpha Particles on Small Mammals, this Symposium.

Stapleton, G. E. (1964), Lethal, Genetic, and Cytogenetic Effects of Fast Charged Particles on Various Biological Materials, this Symposium.

Tochilin, E., J. T. Lyman, F. H. Attix, and E. J. West (1963), The Dose Response of Glass, Thermoluminescent and Film Dosimeters to High Energy Charged Particles, Rad. Res., 19:200.

Wallace, R., P. Steward, and C. A. Sondhaus (1964), Primary- and Secondary-Proton Dose Rates in Spheres and Slabs of Tissue, this Symposium.

Zellmer, R. W., and R. G. Allen (1961), Cosmic Radiation-Laboratory Observations, Symposium Aerospace Radiobiology, Aerospace Med., 32:942-946.

Zellmer, R. W., J. F. Culver, and J. E. Pickering (1962), Proton Irradiation Effects in Primates, 2nd Internat. Congress of Rad. Res., Harrogate, Yorkshire, England.

TYPE OF RADIATION AND EXPERIMENT	MIDPOINT DOSE (rad)	SURVIVAL TIME, DAYS							
GAMMA	AIR →	0	195	340	485	630	775	920	1065
	ABSORBED →	0	125	225	325	425	525	625	725
63M2		S*		S	S	18	10 12	14	11
64M1		S		S	S	16	12	15	11
64M4			S	S	S				
		S	S	S	29				
PROTON	AIR →	0	200	350	500	650	800	950	
	ABSORBED →	0	260	455	650	845	1040	1235	
64M2		S	S	S	S	13	13	10	
64M3		S	S	S	S	19	11	12	
64M5			S	S	S				
		S	S	S	18				

* 30 DAY PERIOD

Table 1. Mortality and survival time in whole body irradiated monkeys.

NATIONAL AERONAUTICS AND SPACE ADMINISTRATION
AMES RESEARCH CENTER, MOFFETT FIELD, CALIFORNIA

MIDPOINT DOSE AIR (rad)	MIDPOINT DOSE ABSORBED (rad)	MAXIMUM WBC DEPRESSION (100-% PRE-EXPOSURE COUNTS) MEAN	(INCIDENCE)
		GAMMA RADIATION	
0	0	17	(16, 18)
195	125	68	(68, 68)
340	225	83	(79, 87, 84)
485	325	90	(90, 93, 86)
		PROTON RADIATION	
0	0	23	(14, 15, 40)
200	260	82	(79, 84, 80, 87)
350	455	92	(95, 93, 86, 93)
500	650	95	(95, 92, 97, 95)

Table 2. Relationship between radiation dose and maximum depression of WBC.

NATIONAL AERONAUTICS AND SPACE ADMINISTRATION
AMES RESEARCH CENTER, MOFFETT FIELD, CALIFORNIA

Table 3.- Relative biological effectiveness of protons and neutrons in large animals.

Biological endpoint	Animal	Radiation type: energy, mev *	Dose, rads **	RBE and/or observations	Exposure geometry ***	Investigator
Lethality	Dog	X:0.25 vs. SFN:9 1 2	MTD(252/289) " (255/289) " (268/289)	0.85(0.95)	BL	Bond, 1956
	Dog	X:0.25 SFN:2	MTD(212/239)	0.9	BL	Alpen, 1960
	Monkey	G:1.2 FN:14	Air(?)(500/393)	1.3	BL(?)	Zellmer, 1962
	Goat	G:2.5 SFN:0.7	MAD(340/460)	0.7	BL	Batchelor, 1964
	Dog	X-ray P:126 240 510	Air(?) " "	1.0 1.15 1.15	? ? ?	Grigor'ev, 1964
	Monkey	G:1.2 P:730	Air(?)(500/312)	1.6	UL(?)	Pickering, 1963
	Monkey	G:1.2 P:200	MTD(325/650) MAD(485/500)	0.5 1	R	Taketa, this study
WBC depression	Monkey	G:1.2 P:200	MTD(190/250) MAD(290/200)	0.7 1.4	R	" "
Erythropoiesis	Dog	X:0.25 SFN:2	MTD(150,4x)	1	X:R, N:BL	Baum, 1961

* X = X-ray, N = neutron (S = simulated, F = fission), G = gamma ray, P = proton

** MTD = midline tissue dose, MAD = midline air dose

*** BL = bilateral, UL = unilateral, R = rotation, X = X-ray, N = neutron

FIGURE LEGENDS

Figure 1.- Monkey positioned for omnidirectional exposure to protons from the Berkeley 184-inch cyclotron. The beam port is seen above the animal.

Figure 2.- Depth-dose energy distribution profile in whole body irradiated monkeys: Protons vs. Gamma Rays. (See text for explanation.) (a) Whole body depth-dose profile. (b) Midaxial dose profile. (c) Cross-sectional depth-dose profile at the midpoint level of the animal.

Figure 3.- Dose-response relationship of white blood cell count in whole body proton irradiated monkeys.

Figure 4.- Changes in white blood cell counts in whole body irradiated monkeys: Protons vs. Gamma Rays. (a) 200 rad air dose. (b) 350 rad air dose. (c) 500 rad air dose.

Figure 5.- Relationship between radiation dose and maximum depression of white blood cells in proton and gamma ray animals. (a) Comparison based on air dose. (b) Comparison based on absorbed tissue dose.

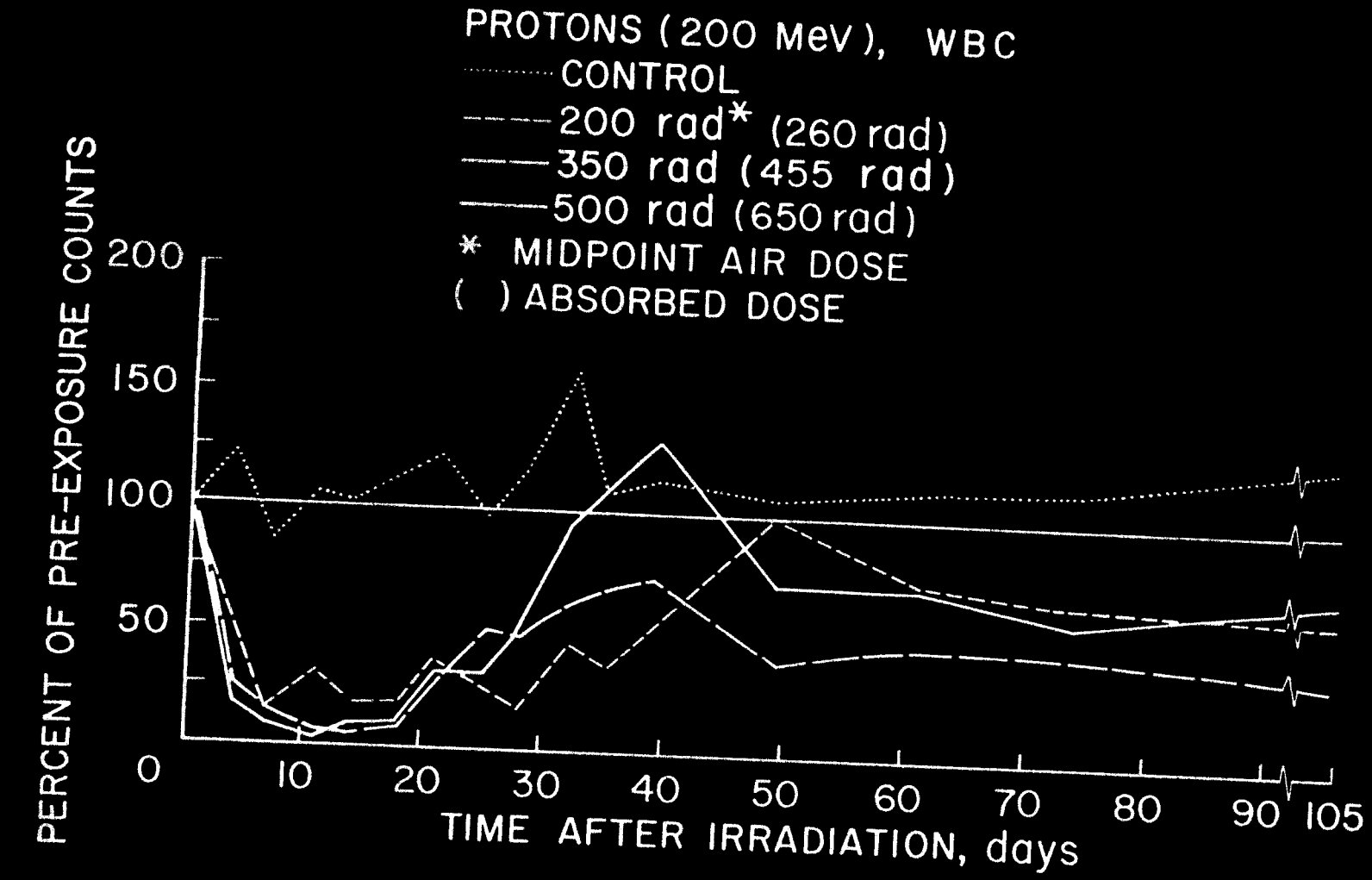
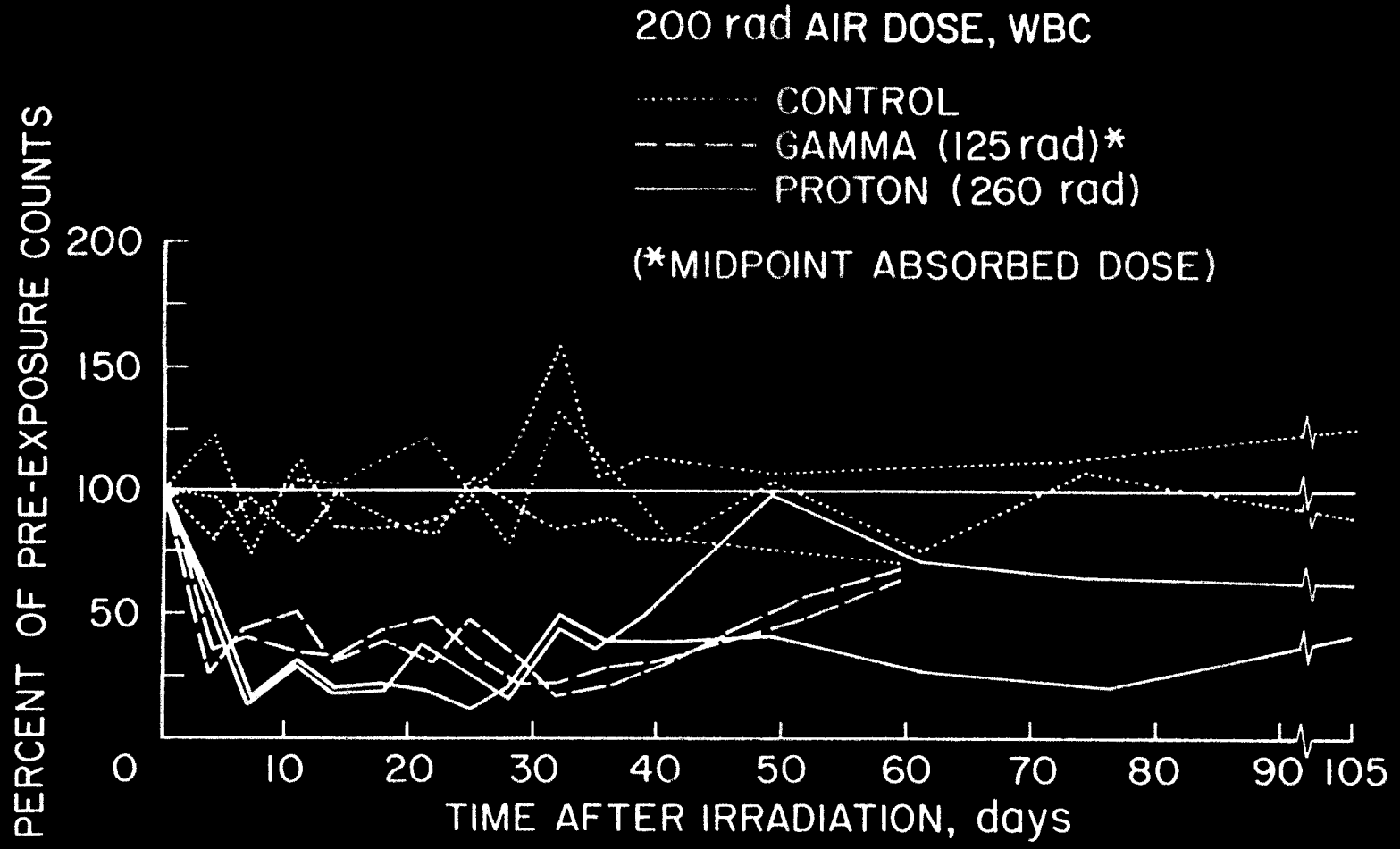
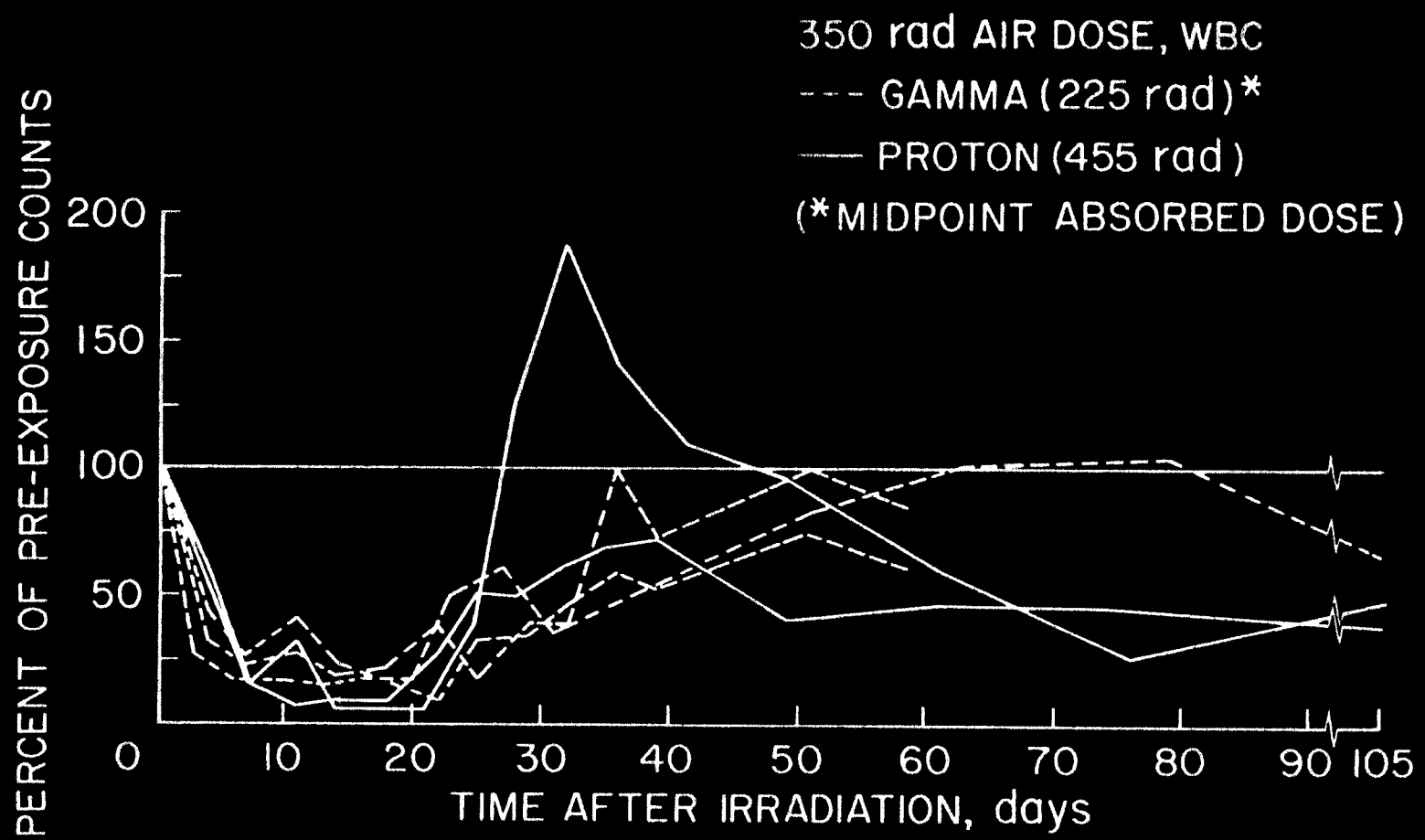


Figure 1. Dose-response relationship of white blood cell counts in whole body proton irradiated monkeys.



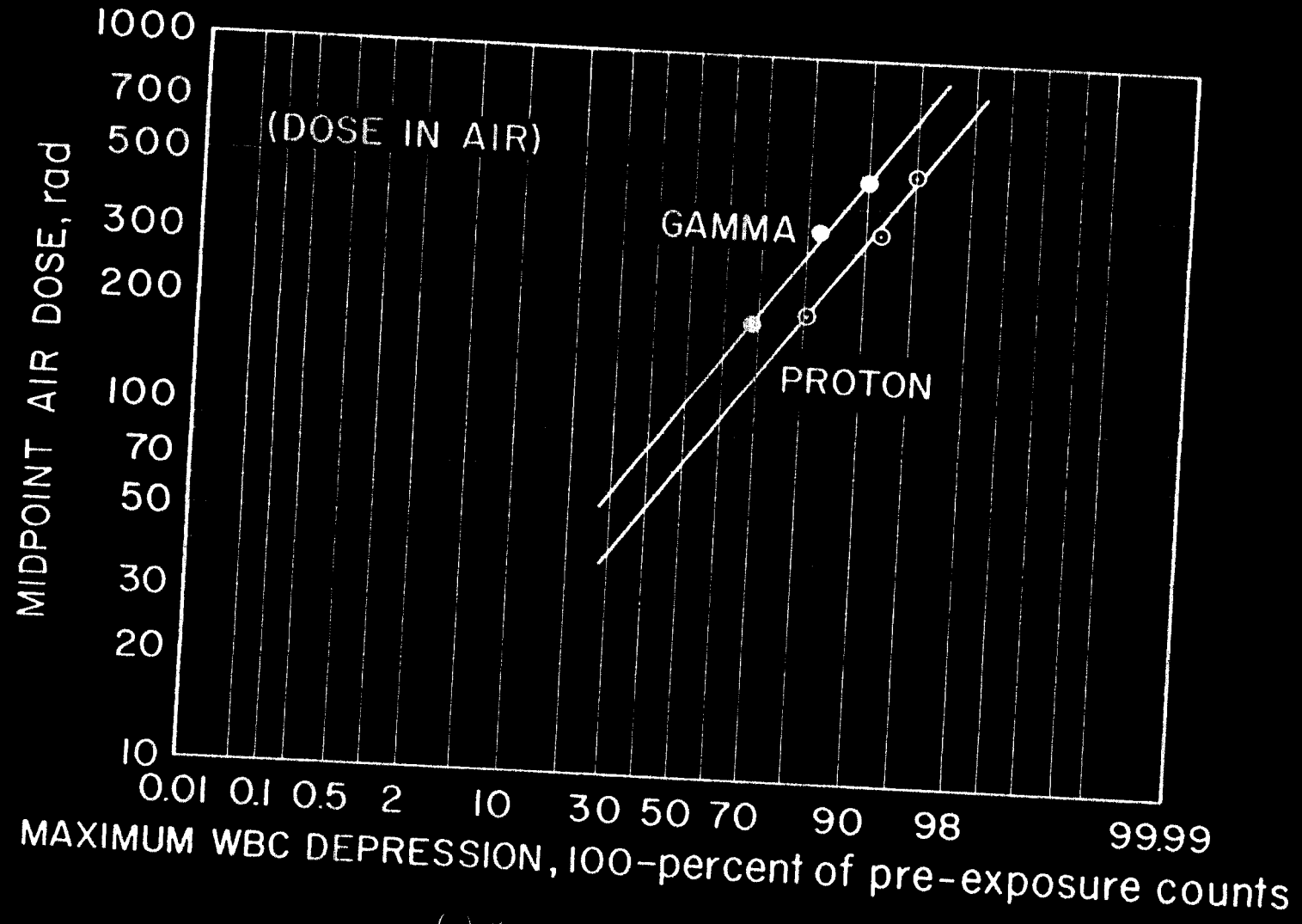
(a) 200 rad air dose.

Figure 7. Changes in white blood cell counts in whole body irradiated monkeys: Protons vs. Gamma Rays.



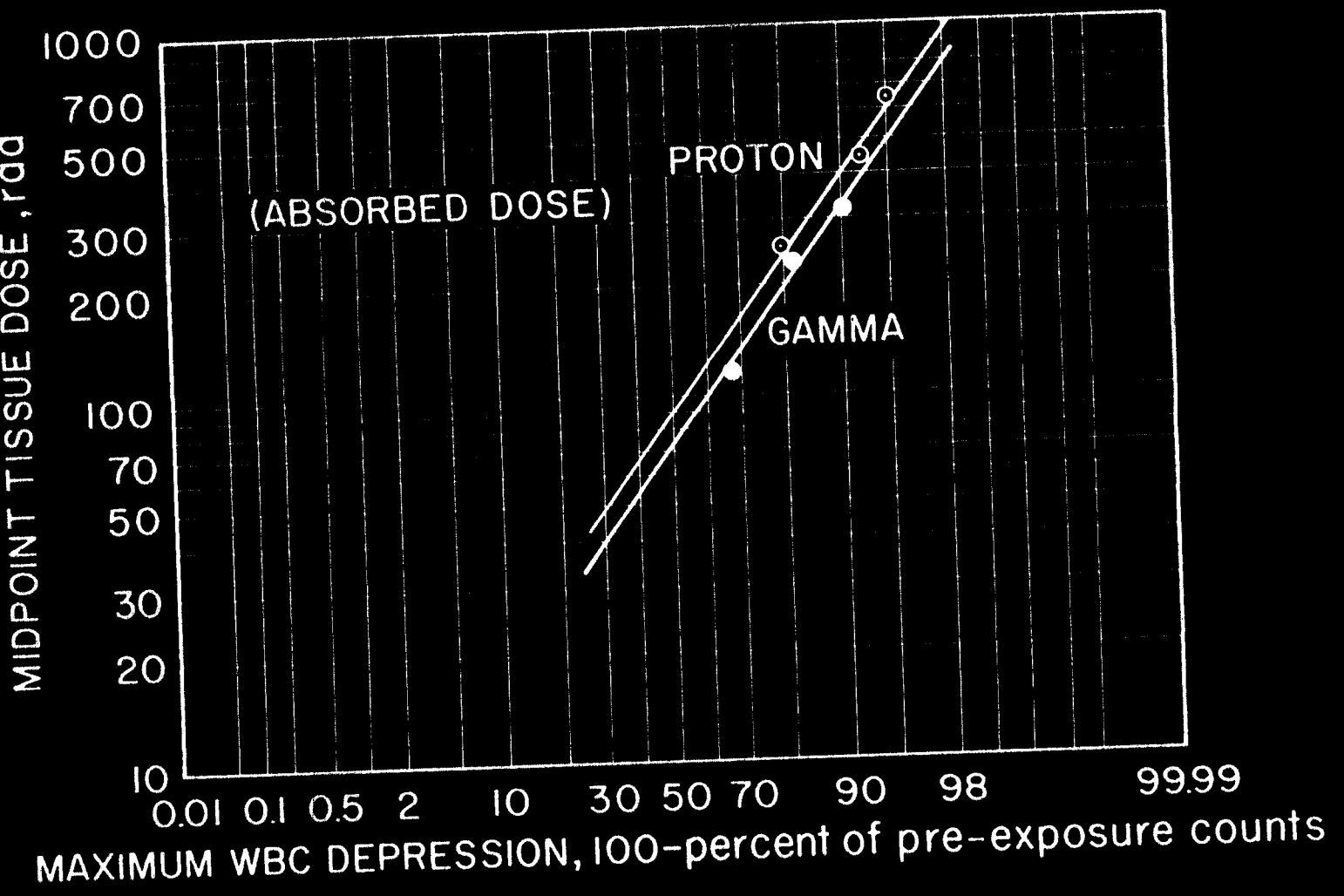
(b) [illegible] rad air dose.

Figure 3. Continued.



(a) Comparison based on air dose.

Figure 4. Relationship between radiation dose and maximum depression of white blood cells in proton and gamma ray animals.



(b) Comparison based on absorbed tissue dose.

Figure 5. Concluded.